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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

JUAN JOSE LEGARDA IBANEZ

Serial No. 10/621,229

Filed: July 15, 2003

For: Flumazenil for the Treatment
of Alcohol Dependency

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Art Unit: 1614

Examiner: Not yet assigned

PETITION TO ACCELERATE EXAMINATION UNDER MPEP 708.02 VIII

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant hereby petitions under MPEP 708.02 VIII to accelerate examination of the above-identified application. Pursuant to this section, Applicant provides the following information.

1) A listing of claims directed to a single invention appears on **Page 2** of this Petition.

2) A statement that a pre-examination search was made, appears on **Page 5** of this Petition. A copy of the search is attached as Exhibit A.

3) A discussion of the references which points out how the subject matter is patentable over the references begins on **Page 6** of this Petition.

03/06/2006 MBIZUNES 00000085 10621229

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I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, VA, 22313-1450, on February 28, 2006.

Handwritten signature of Stephen C. MacDonald
Stephen C. MacDonald, Ph.D. - Reg. No. L0063

Claims Listing

Claims 1-16. (Cancelled)

17. (New) A method for treating alcohol dependency comprising administering an effective amount of flumazenil to a patient in need of treatment,

wherein the flumazenil is administered sequentially in doses between about 0.1 and 0.3 mg of flumazenil at time intervals between about 1 and 15 minutes.

18. (New) The method of claim 17, wherein the effective amount of flumazenil is between about 1.5 and 2.5 mg/day.

19. (New) The method of claim 17, wherein the amount of flumazenil that is administered in each sequential administration is about 0.2 mg.

20. (New) The method of claim 17, wherein the flumazenil is administered at intervals of about 3 minutes.

21. (New) The method of claim 17, wherein the effective amount of flumazenil is about 2 mg/day.

22. (New) The method of claim 17, wherein the flumazenil is administered orally or parenterally.

23. (New) The method of claim 22, wherein the parenteral administration of flumazenil is intravenous administration.

24. (New) The method of claim 17, wherein the flumazenil is administered at doses of about 0.2 mg of flumazenil at intervals of about 3 minutes until an effective amount of flumazenil has been administered.

25. (New) The method of claim 24, wherein the therapeutically effective amount is about 2 mg/day.

26. (New) The method of claim 17, wherein the flumazenil is administered before, during or after treatment with an additional agent.

27. (New) The method of claim 26, wherein the additional agent is clomethiazole.

28. (New) The method of claim 26, wherein the additional agent is selected from the group consisting of Vitamin B Complex, Piracetam, vitamins, minerals, proteins, amino acids, disulfiram, fluoxetine, and combinations thereof.

29. (New) The method of claim 17, wherein the flumazenil is administered under sedation.

30. (New) The method of claim 17, wherein the administration of flumazenil reduces or eliminates the desire to drink alcohol.

31. (New) A method for treating or reducing the symptoms of alcohol withdrawal comprising administering an effective amount of flumazenil, to a patient in need of treatment,

wherein the flumazenil is administered sequentially in doses between about 0.1 and 0.3 mg of flumazenil at time intervals between about 1 and 15 minutes.

32. (New) The method of claim 31, wherein the effective amount of flumazenil is between about 1.5 and 2.5 mg/day.

33. (New) The method of claim 31, wherein the amount of flumazenil that is administered in each sequential administration is about 0.2 mg.

34. (New) The method of claim 31, wherein the flumazenil is administered at intervals of about 3 minutes.

35. (New) The method of claim 31, wherein the effective amount of is about 2 mg/day.

36. (New) The method of claim 31, wherein the flumazenil is administered orally or parenterally.

37. (New) The method of claim 36, wherein the parenteral administration of flumazenil is intravenous administration.

38. (New) The method of claim 31, wherein the flumazenil is administered at doses of about 0.2 mg of flumazenil at intervals of about 3 minutes until an effective amount of flumazenil has been administered.

39. (New) The method of claim 38, wherein the therapeutically effective amount is about 2 mg/day.

40. (New) The method of claim 31, wherein the flumazenil is administered before, during or after treatment with an additional agent.

41. (New) The method of claim 40, wherein the additional agent is clomethiazole.

42. (New) The method of claim 40, wherein the additional agent is selected from the group consisting of Vitamin B Complex, Piracetam, vitamins, minerals, proteins, amino acids, disulfiram, fluoxetine, and combinations thereof.

43. (New) The method of claim 31, wherein the flumazenil is administered under sedation.

44. (New) The method of claim 31, wherein the administration of flumazenil reduces or eliminates the desire to drink alcohol.

45. (New) The method of claim 31, wherein the symptoms are selected from the group consisting of tremor, weakness, sweats, nausea, convulsions, hallucinations, and delirium tremens.

Search Results

Applicant states herein that a pre-examination search was conducted during the international stage of this application PCT/ES02/00008. MPEP 708.02 (VIII) permits the entry of the International Search Report to satisfy this requirement. A copy of the International Search Report is attached as Exhibit A. The articles cited in the International Search Report were disclosed in the Information Disclosure Statement filed May 4, 2005. A supplemental Information Disclosure Statement was filed on September 7, 2005 disclosing further references relevant to this application. Copies of the references were made of record when filing the Information Disclosure Statements.

Discussion of References Cited

International Search Report references

The claims are directed to a method of treating alcohol dependency comprising administering flumazenil in doses between about 0.1 and 0.3 mg of flumazenil at time intervals between about 1 and 15 minutes. GERRA et al. disclose administering flumazenil at doses of 0.5 mg every 6 hours. The articles by NUTT et al., NUTT et al., POTOKAR et al., BUCK et al., and FILE et al. only disclose administering a single dose of flumazenil. None of the references in the Search Report disclose the sequential dosing of flumazenil between about 0.1 and 0.3 mg to treat alcohol dependency.

Supplemental IDS references

There were 92 references cited in the supplemental IDS pertaining generally to the use of flumazenil in conditions other than alcohol dependency, for example, GABA receptor structure and pharmacology.

References 1-4, 6-9, 12, 17, 22, 23, 27, 28, 35, 36, 38, 44, 46-48, 63, 66, 67, 72, 77, 80-82, and 84-87 are not prior art since they were published after the priority date, but illustrate the state of the art.

References 5, 11, 13, 14-16, 21, 24, 25, 26, 30, 31, 33, 34, 37, 39, 40, 50, 51, and 52 provide a characterization of GABA receptor pharmacology pertaining to the effects of ethanol. None of these references disclose the treatment of alcohol dependency comprising administering flumazenil in doses between about 0.1 and 0.3 mg of flumazenil at time intervals between about 1 and 15 minutes.

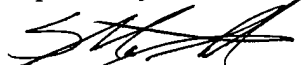
References 75, 76, 78, 79, and 83 provide a characterization of GABA receptors and the properties of the subunits that form the GABA receptors. None of these references disclose the treatment of alcohol dependency comprising administering flumazenil in doses between about 0.1 and 0.3 mg of flumazenil at time intervals between about 1 and 15 minutes.

References 10, 19, 45, 58-62, 64, 65, 68, 69, 71, 73-74, and 88-92 provide a characterization of GABA receptor pharmacology. None of these references disclose treating alcohol dependency comprising administering flumazenil in doses between about 0.1 and 0.3 mg of flumazenil at time intervals between about 1 and 15 minutes.

References 18, 20, 29, 32, 41-43, 49, 53-57, and 70 describe the actions of flumazenil on reducing GABA receptor subunit expression, pain, ethanol intake, ethanol withdrawal syndromes, hyperphagia or anxiety, but do not disclose the treatment of alcohol dependency comprising administering flumazenil in doses between about 0.1 and 0.3 mg of flumazenil at time intervals between about 1 and 15 minutes.

Applicant respectfully requests accelerated prosecution of this application having satisfied the requirements of MPEP 708.02 (VIII). Form PTO-2038 is enclosed herewith authorizing the charge of \$130.00 for the fee required under 37 C.F.R. §1.17 (h). The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 11-0855.

Respectfully submitted,



Stephen C. MacDonald, Ph.D.
Patent Agent
Reg. No. L0063

Kilpatrick Stockton LLP
1100 Peachtree Street
Suite 2800
Atlanta, Georgia 30309-4530
Our Docket: 55979-0100(314589)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/ES 02/00008

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 : A61P 25/32, A61K 31/5517

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 :

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC, WPI, REGISTRY, CA, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GERRA, G. y col. Effectiveness of Flumazenil in the treatment of ethanol withdrawal. Current Therapeutic Research. Julio 1991, Vol. 50, Nº 1, pages 62-66	1-16
X	NUTT, D. y col. Flumazenil in alcohol withdrawal. Alcohol & Alcoholism. 1992, suppl 2, pages 337-341, ISSN 0735-0414	1-16
X	NUTT, D. y col. Benzodiazepine Receptors in alcohol withdrawal neuroschycho pharmacology. May 1994, Vol. 10, nº 35, part 1.	1-16

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

05 April 2002 (05.04.02)

Date of mailing of the international search report

25 April 2002 (25.04.02)

Name and mailing address of the ISA/ S.P.T.O.

Authorized officer

Facsimile No.

Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/ES 02/00008

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	POTOKAR, J. y col. Flumazenil in alcohol withdrawal: a double-blind placebo-controlled study. Alcohol & Alcoholism. 1997, Vol. 32, Nº 5, pages 605-611, ISSN 0735-0414. Abstract	1-16
X	BUCK, K.J. y col. Reversal of alcohol dependence and tolerance by a single administration of flumazenil ¹ . The Journal of pharmacology and Experimental Therapeutics. 1991, Vol. 257, Nº 3, pages 984-989, ISSN 0022-3565. Abstract	1-16
X	FILE, S.E. y col. Effects of Nitrendipine, Chlordiazepoxide, Flumazenil and Baclofen on the increased anxiety resulting from alcohol withdrawal. Prog. Neuro-Psychopharmacol & Biol. Psychiatry. 1992, Vol.16, Nº 1, pages 87 -93, ISSN 0278- 5846. Abstract and conclusions.	1-16

INTERNATIONAL SEARCH REPORT

International application No.

PCT/ES 02/00008

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9-16
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 9-16 relate to a therapeutic treatment of the human body. Notwithstanding, the search relating to said claims was carried out and was based on the alleged effects of the compound.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INFORME DE BUSQUEDA INTERNACIONAL

Solicitud internacional n°

PCT/ES 02/00008

A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD

 CIP⁷ A61P 25/32, A61K 31/5517

De acuerdo con la Clasificación Internacional de Patentes (CIP) o según la clasificación nacional y la CIP.

B. SECTORES COMPRENDIDOS POR LA BÚSQUEDA

 Documentación mínima consultada (sistema de clasificación, seguido de los símbolos de clasificación)
 CIP⁷

Otra documentación consultada, además de la documentación mínima, en la medida en que tales documentos formen parte de los sectores comprendidos por la búsqueda

Bases de datos electrónicas consultadas durante la búsqueda internacional (nombre de la base de datos y, si es posible, términos de búsqueda utilizados)

EPODOC, WPI, REGISTRY, CA, MEDLINE, BIOSIS

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría *	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante para las reivindicaciones n°
X	GERRA, G. y col. Effectiveness of Flumazenil in the treatment of ethanol withdrawal. Current Therapeutic Research. Julio 1991, Vol. 50, N° 1, páginas 62-66	1-16
X	NUTT, D. y col. Flumazenil in alcohol withdrawal. Alcohol & Alcoholism. 1992, suppl 2, páginas 337-341, ISSN 0735-0414	1-16
X	NUTT, D. y col. Benzodiazepine Receptors in alcohol withdrawal neuroschycho pharmacology. Mayo 1994, Vol. 10, n° 35, part 1.	1-16

☒ En la continuación del recuadro C se relacionan otros documentos ☐ Los documentos de familia de patentes se indican en el anexo

* Categorías especiales de documentos citados:

"A" documento que define el estado general de la técnica no considerado como particularmente relevante.

"E" solicitud de patente o patente anterior pero publicada en la fecha de presentación internacional o en fecha posterior.

"L" documento que puede plantear dudas sobre una reivindicación de prioridad o que se cita para determinar la fecha de publicación de otra cita o por una razón especial (como la indicada).

"O" documento que se refiere a una divulgación oral, a una utilización, a una exposición o a cualquier otro medio.

"P" documento publicado antes de la fecha de presentación internacional pero con posterioridad a la fecha de prioridad reivindicada.

"T" documento ulterior publicado con posterioridad a la fecha de presentación internacional o de prioridad que no pertenece al estado de la técnica pertinente pero que se cita por permitir la comprensión del principio o teoría que constituye la base de la invención.

"X" documento particularmente relevante; la invención reivindicada no puede considerarse nueva o que implique una actividad inventiva por referencia al documento aisladamente considerado.

"Y" documento particularmente relevante; la invención reivindicada no puede considerarse que implique una actividad inventiva cuando el documento se asocia a otro u otros documentos de la misma naturaleza, cuya combinación resulta evidente para un experto en la materia.

"&" documento que forma parte de la misma familia de patentes.

Fecha en que se ha concluido efectivamente la búsqueda internacional. 5 abril 2002 (05.04.2002)

Fecha de expedición del informe de búsqueda internacional

29 ABR 2002

29.04.02

 Nombre y dirección postal de la Administración encargada de la búsqueda internacional O.E.P.M.
 5 abril 2002 (05.04.2002)

Funcionario autorizado

E. ALBARRÁN

 C/Panamá, 1, 28071-Madrid, España.
 n° de fax +34 91 3495304

n° de teléfono + 34 91 34 95595

INFORME DE BUSQUEDA INTERNACIONAL

Solicitud internacional n°

PCT/ES 02/00008

C (Continuación). DOCUMENTOS CONSIDERADOS RELEVANTES		
Categoría *	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante p
X	POTOKAR, J. y col. Flumazenil in alcohol withdrawal: a double-blind placebo-controlled study. Alcohol & Alcoholism. 1997, Vol. 32, N° 5, páginas 605-611, ISSN 0735-0414. Resumen	1-16
X	BUCK, K.J. y col. Reversal of alcohol dependence and tolerance by a single administration of flumazenil. The Journal of pharmacology and Experimental Therapeutics. 1991, Vol. 257, N° 3, páginas 984-989, ISSN 0022-3565. Resumen	1-16
X	FILE, S.E. y col. Effects of Nitrendipine, Chlordiazepoxide, Flumazenil and Baclofen on the increased anxiety resulting from alcohol withdrawal. Prog. Neuro-Psychopharmacol & Biol. Psychiatry. 1992, Vol.16, N° 1, páginas 87 -93, ISSN 0278- 5846. Resumen y conclusiones	1-16

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional n°

PCT/ES 02/00008

Recuadro I Observaciones cuando se estime que algunas reivindicaciones no pueden ser objeto de búsqueda (Continuación del punto 2 de la primera hoja)

De conformidad con el artículo 17.2.a), algunas reivindicaciones no han podido ser objeto de búsqueda por los siguientes motivos:

1. ☒ Las reivindicaciones n°: 9-16 se refieren a un objeto con respecto al cual esta Administración no está obligada a proceder a la búsqueda, a saber: las reivindicaciones 9-16 se refieren a un método de tratamiento terapéutico aplicado al cuerpo humano; a pesar de ello, la búsqueda se ha realizado para dichas reivindicaciones en base a los efectos atribuidos al compuesto.
2. ☐ Las reivindicaciones n°: se refieren a elementos de la solicitud internacional que no cumplen con los requisitos establecidos, de tal modo que no pueda efectuarse una búsqueda provechosa, concretamente:
3. ☐ Las reivindicaciones n°: son reivindicaciones dependientes y no están redactadas de conformidad con los párrafos segundo y tercero de la regla 6.4.a).

Recuadro II Observaciones cuando falta unidad de invención (Continuación del punto 3 de la primera hoja)

La Administración encargada de la Búsqueda Internacional ha detectado varias invenciones en la presente solicitud internacional, a saber:

1. ☐ Dado que todas las tasas adicionales han sido satisfechas por el solicitante dentro del plazo, el presente informe de búsqueda internacional comprende todas las reivindicaciones que pueden ser objeto de búsqueda.
2. ☐ Dado que todas las reivindicaciones que pueden ser objeto de búsqueda pueden serlo sin un esfuerzo particular que justifique una tasa adicional, esta Administración no ha invitado al pago de ninguna tasa de esta naturaleza.
3. ☐ Dado que tan sólo una parte de las tasas adicionales solicitadas ha sido satisfecha dentro del plazo por el solicitante, el presente informe de búsqueda internacional comprende solamente aquellas reivindicaciones respecto de las cuales han sido satisfechas las tasas, concretamente las reivindicaciones n°:
4. ☐ Ninguna de las tasas adicionales solicitadas ha sido satisfecha por el solicitante dentro de plazo. En consecuencia, el presente informe de búsqueda internacional se limita a la invención mencionada en primer término en las reivindicaciones, cubierta por las reivindicaciones n°:

Indicación en cuanto a la reserva

- ☐ Las tasas adicionales han sido acompañadas de una reserva por parte del solicitante.
- ☐ El pago de las tasas adicionales no ha sido acompañado de ninguna reserva.